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How do type of preoperative P2Y12 receptor inhibitor and withdrawal time affect bleeding – protocol of a systematic review and individual patient data meta-analysis.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060404
Article Type:	Protocol
Date Submitted by the Author:	20-Dec-2021
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Keywords:	Cardiothoracic surgery < SURGERY, Anaesthesia in cardiology < ANAESTHETICS, Coronary heart disease < CARDIOLOGY

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How do type of preoperative P2Y$_{12}$ receptor inhibitor and withdrawal time affect bleeding – protocol of a systematic review and individual patient data meta-analysis.

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Word count 2361

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ABSTRACT

Introduction In order to reduce the risk of bleeding in patients on P2Y$_{12}$ receptor inhibitors presenting for non-emergent coronary artery bypass grafting (CABG), current guidelines recommend a preoperative discontinuation period of at least three, five and seven days for ticagrelor, clopidogrel, and prasugrel, respectively, to allow for recovery of platelet function. However, there is still substantial inter-institutional variation in preoperative management and relevant covariates of CABG-related bleeding are largely elusive so far.

Methods and analysis We search PubMed (July 2013 to November 2021) and EMBASE (January 2014 to November 2021) using the following terms, MeSH terms and their synonyms: clopidogrel, prasugrel, ticagrelor, dual antiplatelet, P2Y$_{12}$ receptor inhibitor, CABG, bleeding, haemorrhage. Two independent reviewers screen all abstracts and full paper for eligibility. Disagreements are solved by consulting with a third reviewer.

The primary outcome is the incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding depending on type of P2Y$_{12}$ receptor inhibitor and preoperative withdrawal period. The secondary outcomes are mortality and myocardial infarction. We will perform an individual patient data meta-analysis and adjust for demographic and procedural variables. Subgroup analysis will be performed for anaemic patients and patients undergoing non-emergent versus urgent/emergent surgery.

Ethics and dissemination This review will provide a comprehensive overview on how type of preoperative P2Y$_{12}$ receptor inhibitor and withdrawal time affect incidence of BARC-4 bleeding accounting for relevant covariates and subgroups.

PROSPERO registration number: is not yet available but will follow as soon as possible

Strengths and Limitations

- Despite existing guidelines there is substantial heterogeneity in preoperative management of patients undergoing coronary artery bypass grafting (CABG) in patients on dual antiplatelet therapy, and there is difference and heterogeneity in reported incidence of CABG-related bleeding.

- Bleeding academic research consortium (BARC) bleeding has been introduced as a standardized bleeding definition for patients on antithrombotic therapy.

- This individual patient data meta-analysis will incorporate data from patients undergoing CABG during dual antiplatelet therapy to assess the incidence of CABG-related bleeding, defined as BARC-4 bleeding, and the potential impact of relevant covariates and subgroups in addition to type of $P2Y1_2$ receptor inhibitor and preoperative withdrawal time.

- The individual patient data meta-analysis will be performed with all data available. It cannot be ruled out that some studies are not included. If we cannot get individual patient data for all identified studies, the risk of availability bias will be assessed by comparing study characteristics of those providing data and those that do not.

- It is possible that in some studies not all information to calculate BARC-4 bleeding and the exact preoperative drug withdrawal period will be available. Every attempt will be made to obtain these data.

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BACKGROUND

In the 54 European Society of Cardiology (ESC) member countries 34.9 million people live with ischemic heart disease in 2017. The median age-standardized prevalence per 1,000,000 inhabitants of each member country was 2270 (IQR 1508-2565) and was lower for females compared with males. In the 2018/19 survey, these figures translated into a median of 2047 (IQR 1478-2588) percutaneous coronary interventions and 301.1 (IQR 245.0-440.0) coronary artery bypass grafting operations (CABGs) per one million inhabitants.[1]

Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ receptor inhibitor on top of aspirin is the cornerstone to prevent thrombotic complications in patients with acute coronary syndromes (ACS) and/or after percutaneous coronary interventions with stents, albeit at the risk of increased bleeding.[2 3 4 5]

Large observational studies have demonstrated an association between the severity of cardiac surgery-related bleeding and 30-day postoperative morbidity and mortality.[6-10] A sub-study of the Transfusion Avoidance in Cardiac Surgery study (TACS) demonstrated that two consensus-based scoring systems for assessing the severity of bleeding, the Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery (UDPB) and the European Coronary Artery Bypass Graft (E-CABG), performed well in predicting 28-day mortality. Specifically, severe bleeding defined as either UDPB class 3 or E-CABG grade 2, both of which comprise transfusion of ≥ 5 units of red blood cells, was associated with about 40% relative increased risk of mortality.[6] Suggested mechanisms for bleeding associated mortality are organ dysfunctions triggered by decreased oxygen delivery and hypotension following major blood loss in patients with atherosclerotic disease and adverse effects of transfusion.[11 12] Preventing perioperative blood loss may be more efficacious in improving outcome than mere reduction of allogenic blood components.[7]

Currently, almost 11% of patients presenting with ACS have to undergo aorto-coronary bypass grafting during DAPT.[13]

In order to reduce the risk of bleeding in patients on $P2Y_{12}$ receptor inhibitors presenting for non-emergent cardiac surgery, current European Society of Cardiologist (ESC) and American Heart Association / American College of Cardiology (AHA / ACC) guidelines recommend a "standardized" preoperative discontinuation period of at least three days for ticagrelor, five days for clopidogrel, and seven days for prasugrel (II a recommendation) to allow for recovery of platelet function.[2 14 15] However, there is still substantial interinstitutional variation in preoperative management of ACS patients on DAPT, and there is heterogeneity in definition and incidence of bleeding. Moreover, data on prasugrel are sparse [7 16].

Two big registries used different bleeding definitions to evaluate the overall incidence of major CABG-related bleeding in patients on clopidogrel as compared to ticagrelor and the specific impact of preoperative withdrawal time.[8 9] The Swedish registry including 2,244 patients with ACS who underwent CABG demonstrated a 5% lower incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding in patients on ticagrelor as compared to clopidogrel (12.9% vs 17.6%, p=0.033). This difference was mainly driven by a sharp decline in bleeding after 72 hours withdrawal of ticagrelor as compared with a more gradual decrease with clopidogrel. Importantly, incidence of BARC-4 bleeding was 38 and 31% when ticagrelor / clopidogrel was discontinued less than 24 hours, preoperatively.[8] In contrast, a subgroup analysis of 1,376 patients from the E-CABG registry demonstrated a similar incidence of severe or massive UDPB (11.2% vs 8.7%, p=0.14) and BARC-4 bleeding (13.2% vs 11.6%, p=0.38) in clopidogrel and ticagrelor treated patients, and a similar decrease in bleeding with increasing days off $P2Y_{12}$ receptor inhibitors, compatible with time-dependent recovery of platelet function. In a propensity score-matched analysis, 4 to 5 days off clopidogrel reduced

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severe / massive UDPB class by 7.3% as compared to a 3 days preoperative withdrawal period (p=0.031). Similarly, 3 days off ticagrelor reduced bleeding by 13.3% as compared to a 0-2 days preoperative withdrawal period (p=0.003).[9]

However, the additional impact of covariates known to affect CABG-related bleeding, the potential bias introduced by preoperative anaemia, occurring in up to 40% of patients undergoing cardiac surgery, and the incidence of myocardial infarction in this particular patient population remain largely elusive so far.[17-21]

The proposed review is therefore needed to determine the effect of preoperative $P2Y_{12}$ receptor inhibitors and time of preoperative withdrawal in patients undergoing on-pump CABG on primary (BARC-4 bleeding) and secondary outcomes (all-cause mortality and myocardial infarction) in studies published from July 2013 to November 2021. Studies published until June 2013 have been included in a prior pooled meta-analysis which demonstrated that late preoperative discontinuation of $P2Y_{12}$ receptor inhibitors (< 5 days) was associated with a 2.5- and 1.5- fold increased risk of reoperation for bleeding and death, respectively as compared to early (≥ 5 days) preoperative discontinuation.[21]

Although not yet validated regarding the risk of CABG-associated morbidity and mortality, we decided to use the BARC-4 bleeding definition because BARC bleeding has been introduced as a standardized bleeding endpoint for patients receiving antithrombotic therapy.[22]

To fill the gaps in the knowledge as outlined above we aim to conduct an individual patient data (IPD) meta-analysis (MA). The primary objective is to assess the incidence of BARC-4 bleeding depending on type of $P2Y_{12}$ receptor inhibitors and preoperative withdrawal period. Furthermore, the effect of preoperative $P2Y_{12}$ receptor inhibitors on in-hospital / 30-day all-cause mortality and myocardial infarction in on-pump CABG patients will be evaluated. We will correct for demographic and procedural variables and

we will perform subgroup analysis to identify the influence of preoperative anaemia and non-emergent CABG vs urgent / emergent CABG and on outcome.

METHODS AND ANALYSES

The review will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[23] The PRISMA-P flow diagram will be used to indicate each step of the review process (figure 1).

Sources of evidence and search strategy

We search PubMed (July 2013 to November 2021, search strategy see table 1) and EMBASE (2014 to 2021, search strategy see table 2) for a combination of terms, MeSH terms and their synonyms in titles and abstracts like 'clopidogrel', 'prasugrel', 'ticagrelor', 'dual antiplatelet', 'P2Y$_{12}$ receptor inhibitor', 'CABG', 'bleeding', 'haemorrhage'. Vocabulary and syntax are adjusted across databases. This strategy was reviewed by a librarian of the Medical University of Graz (AS). Two researchers (IL, MS) search separately according to the search strategy as described in table 1 and 2. We also search the Cochrane Library and carry out a hand search. Unpublished ongoing clinical studies are searched from WHO International Clinical Trials Registry Platform (ICTRP), Clinicaltrails.gov and Prospero (until November 2021).

Table 1 Search strategy for PubMed	
ID	Query
#1	(clopidogrel OR Prasugrel OR Ticagrelor OR dual antiplatelet OR dual-antiplatelet OR P2Y12 receptor inhibitor OR p2y12 receptor antagonist OR p2y12 Inhibitor OR p2y12-inhibitor OR P2Y12 inhibit* OR P2Y12-Inhibit* OR platelet aggregation inhibitor* OR thienopyridine OR ADP receptor blocking agent OR ADP receptor antagonist OR ADP-receptor antagonist OR Adenosine diphosphate receptor antagonist OR ADP-Receptor* OR ADP Receptor* OR Purinergic P2Y Receptor Antagonists [MeSH])
#2	(cabg OR cardiac surgery OR coronary artery bypass OR Coronary artery surgery

	OR coronary surgery OR Coronary bypass surgery OR heart surgery OR "on pump" OR on-pump OR Coronary revascularization OR Coronary revascularisation OR myocardial revascularization OR myocardial revascularisation OR ((coronary OR cardiac) AND (bypass OR surgery OR surgical OR operation OR operative)) OR Coronary Artery Bypass [MeSH] OR myocardial revascularization [MeSH])
#3	(bleeding OR bleed* OR hemorrhage OR hemorrhag* OR haemorrhage OR haemorrhag* OR barc OR Blood loss OR Blood Loss, Surgical [MeSH] OR hemorrhage [MeSH Terms])
#4	#1 AND #2 AND #3
#5	#4 AND July 2013 - November 2021
#6	#5 AND English

Table 2 Search strategy for Embase	
ID	Query
#1	clopidogrel OR Prasugrel OR Ticagrelor OR dual antiplatelet* OR dual-antiplatelet* OR P2Y12 receptor inhibitor OR p2y12 receptor antagonist OR p2y12 Inhibitor OR p2y12-inhibitor OR P2Y12 inhibit* OR P2Y12-Inhibit* OR platelet aggregation inhibitor* OR thienopyridine* OR ADP receptor blocking agent* OR ADP receptor antagonist* OR ADP-receptor antagonist* OR Adenosine diphosphate receptor antagonist OR ADP-Receptor* OR ADP Receptor*
#2	cabg OR cardia* surg* OR coronary artery bypass OR Coronary artery surg* OR coronar* surg* OR Coronary bypass surg* OR heart surg* OR on pump OR on-pump OR Coronar* revasculari* OR myocardial revasculari*
#3	bleed* OR hemorrhag* OR haemorrhag* OR barc OR Blood los*
#4	Blood adj3 los
#5	#3 OR #4
#6	#1 AND #2 AND #5
#7	#6 AND English language
#8	#7 AND 2014 - current

Inclusion and exclusion criteria

We include randomized controlled trials (RCTs) and observational trials that evaluate the effect of different P2Y$_{12}$ receptor inhibitors (clopidogrel, prasugrel and ticagrelor) and drug-free period prior to surgery on any of the defined outcome measures (BARC-4 bleeding, mortality, non-fatal myocardial infarction), to assess differences depending on

1. the individual P2Y$_{12}$ receptor inhibitor and

2. preoperative withdrawal time.

We include adult female and male patients of any age undergoing on-pump CABG during dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel or ticagrelor).

Inclusion criteria are:

- full text articles in English

- Isolated on-pump CABG

- Patients on DAPT (irrespective of type of $P2Y_{12}$ inhibitor) with the discontinuation period being equal to or shorter than 7 days

- At least one BARC-4 criteria documented

Exclusion criteria are:

- Off-pump CABG

- Complex surgery (e.g., CABG + valve)

- Timing of surgery based on preoperative platelet function

Intervention

Intervention: CABG with a preoperative withdrawal time of $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel or ticagrelor) shorter than suggested by ESC and AHA / ACC guidelines

Comparison: CABG with a preoperative withdrawal period of $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel or ticagrelor) according to the ESC and AHA / ACC and guidelines.

Outcomes

Primary outcome

- BARC-4 bleeding

Secondary outcomes

- Mortality (in-hospital mortality/ 30-day mortality)

- Non-fatal myocardial infarction according to the 4th universal definition of MI and

to definitions used in studies included in this meta-analysis.[24]

Languages

English

Time

Study start 04 2021; anticipated study end 03/2023

Study records

Data management

All search results are downloaded into a compatible version of MS Excel (MS Office

Professional Plus 2016) from the interfaces. We transfer these results into a common

Excel file for deduplication. For manual deduplication we have two criteria, title and

author, to unambiguously recognize duplicates. Finally, we do a cross check of the

number of included studies. This data is saved in a password protected online-platform

of the Medical University of Graz with access only for EM, MS, IL and GP.

Selection process

Using the results of the above searches, two authors (IL and MS) independently screen

all titles and abstracts for eligibility. Each of the two authors documents the reason for

exclusion of each trial to be excluded. All records deemed potentially relevant by at least

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one author are obtained in full text format and assessed according to eligibility criteria independently by IL and MS. In a second step these evaluations are discussed with a third researcher (EM) to resolve disagreements. The selection process is plotted in a flow diagram in accordance with the PRISMA statement (figure 1).[25]

Data extraction and management

We independently extract study characteristics such as study design (RCTs, observational trials), authors, year of publication and setting of study. We aim to perform an individual patient data meta-analysis (IPD MA) for the review questions because the main outcome of interest, BARC-4 bleeding, is not generally reported in the literature. IPD MA would furthermore allow for the direct incorporation of demographic and procedural variables, previously identified as potential confounders of increased bleeding into the analysis. [7 16 26]

Following the selection process, we address the first author and only if unavailable the corresponding author of each identified study. All authors are asked to provide a selection of parameters from their original data sets in a pseudonymized fashion that does not allow identification of individual identities. We provide an Excel sheet outlining the requested parameters (see table 3).

Table 3 Parameters requested from individual studies

	Parameter	Categories/Unit
	Age[1]	years
	Gender[1]	m/f
	Weight	kg
	Height	m
demographics	BMI	kg/m²
	Creatinine	mg/dl or µmol/l
	Creatinine clearance[1]	ml/min
	Diabetes mellitus	y/n
	Liver disease	y/n
	LVEF[1]	%
	Euroscore 2	
	UFH or LMWH or fondaparinux	y/n

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	(within 24 hours preop)	
Procedural variables	Urgency[1]	Elective/urgent/emergency/salvage
	CABG indication	Stable CAD/NSTEMI/STEMI
	CPB time	minutes
	Number of arterial grafts	
	Number of distal anastomoses	
	Tranexamic acid during surgery	y/n
	Hb preoperative	g/l
	Platelets preoperative	$\times 10^9$/l
	Institutional protocol for treating postpump bleeding	y/n
	ASS perioperative continuation	y/n
	ASS cessation prior to surgery	days
	Clopidogrel preoperative	y/n
	Clopidogrel cessation prior to surgery	days
	Prasugrel preoperative	y/n
	Prasugrel cessation prior to surgery	days
	Ticagrelor preoperative	y/n
	Ticagrelor cessation prior to surgery	days
outcome	Chest tube drainage volume within 24h[2]	ml
	Reoperation due to bleeding	y/n
	Intracranial bleeding within 48h hours perioperatively	y/n
	Number of transfused red blood cell units within 48 Hours from incision	
	Postoperative MI	y/n
	In hospital mortality	y/n
	30 day mortality	y/n

*Calculated parameter, [1]part of euroscore II, [2]if unavailable chest tube drainage volume obtained during shorter observation period (define observation period)

Plausibility checks of the received data will be performed by comparing summary measures of the IPD with the published data as well as by checking plausibility of the individual values in a clinical context. Any implausibilities will be resolved with the original authors through queries.

Risk of bias

Two authors (IL, MS) will assess the risk of bias for each trial independently. Possible disagreements will be resolved by consensus, or with consultation of a third party (EM). For RCTs, we will assess risk of bias using the Cochrane Collaboration's tool.[27] We will use the following bias criteria:

- random sequence generation (selection bias)

- allocation concealment (selection bias)

- blinding (performance bias and detection bias), separately for blinding of participants and personnel and blinding of outcome assessment

- incomplete outcome data (attrition bias)

- selective reporting (reporting bias)

- other bias.

We will judge risk of bias criteria as 'low risk', 'high risk' or 'unclear risk' and use individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions.[27]

For observational studies the quality of each study will be assessed using the Robins-I Tool as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[27]

The following domains will be assessed:

- bias due to confounding

- bias in selection of participants into the study

- bias in classification of interventions

- bias due to deviations from intended interventions

- bias due to missing data

- bias in measurement of outcomes

- bias in selection of the reported result.

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Data synthesis

The primary analysis will be performed as a two-stage IPD meta-analysis. For this approach, each study will first be individually analysed according to a pre-specified regression model including parameters of interest (type of $P2Y_{12}$ inhibitor and preoperative withdrawal time) as well as relevant confounders (see table 3). The results of these analyses will be presented as odds ratios (OR) and 95% confidence intervals (CI) and can be displayed in a forest plot. For the second stage, these results will be pooled using standard meta-analytic methods, in our case random-effects models.

If we cannot get individual patient data for all identified studies, the risk of availability bias will be assessed by comparing study characteristics of those providing data and those that do not. Furthermore, the equivalent to the well-known Funnel plot can be visually assessed.

Additionally, subgroup analyses are planned for:

- patients undergoing non-emergent CABG vs patients undergoing urgent / emergent CABG because of ACS and

- patients preoperatively presenting with anaemia according to the World Health Organization-definition of less than 13 g / dL for men and less than 12 g / dL for women vs preoperatively non-anaemic patients.

The analyses will be performed using R version 4.0.3. No imputation for missing data is planned. The analyses are performed in accordance with the handbook of the Cochrane collaboration and results will be presented according to the PRISMA-IPD statement.

Legend to figure 1 Flow chart diagram presenting the selection of articles for systemic review and meta-analysis of preoperative $P2Y_{12}$ receptor inhibitors and incidence of

BARC-4 bleeding depending on type of P2Y$_{12}$ receptor inhibitor and preoperative

withdrawal period.

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Ethics and dissemination

No ethics approval is sought as no original data will be generated for this review.

Findings will be disseminated through peer-reviewed publication and conference

presentation

Contributors

Michael Schoerghuber: study design, bibliographic research, design of data entry forms,

data management, conduct of study, protocol and manuscript writing.

Pregartner: study design, data management, statistical analysis protocol and manuscript

writing and review

Berghold: study design, data management, study design, data management, statistical

analysis protocol and manuscript review

Lindenau: bibliographic, design of data entry forms, data management, conduct of study,

protocol and manuscript review

Zweiker: Scientific coordination, protocol and manuscript writing and review

Voetsch: Scientific coordination, protocol and manuscript review

Mahla: study design, Scientific coordination protocol and manuscript writing and review

Zirlik: Scientific coordination, protocol and manuscript review

Funding

This research received no specific grant from any funding agency in the public,

commercial or not-for-profit sectors

Competing interests

Michael Schoerghuber no conflicts of interest

Gudrun Pregartner no conflicts of interest

Andrea Berghold no conflicts of interest

Ines Lindenau no conflicts of interest

Robert Zweiker no conflicts of interest

Andreas Voetsch no conflicts of interest

Elisabeth Mahla no conflicts of interest

Andreas Zirlik received honoraria for lectures and consulting of Daiichi Sankyo, Lilly,

AstraZeneca, Bristol Myers Squibb, Pfizer, Bayer, Boehringer Ingelheim

Patient and public involvement

Patients and /or the public were not involved in the design, or conduct, or reporting or

dissemination plans of this research

Patient consent for publication

Not applicable

Provenance and peer review

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6,7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7,8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	7, Tab1,2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7,9-10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9,10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	11,12
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	12
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	12
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	12
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	12
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	12

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	n/a
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	n/a
Study characteristics	17	Cite each included study and present its characteristics.	n/a
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	n/a
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	n/a
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	n/a
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	n/a
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	n/a
	23b	Discuss any limitations of the evidence included in the review.	n/a
	23c	Discuss any limitations of the review processes used.	n/a
	23d	Discuss implications of the results for practice, policy, and future research.	n/a
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	n/a

PRISMA 2020 Checklist

BMJ Open

How do type of preoperative P2Y12 receptor inhibitor and withdrawal time affect bleeding? – protocol of a systematic review and individual patient data meta-analysis.

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Manuscripts

How do type of preoperative P2Y$_{12}$ receptor inhibitor and withdrawal time affect bleeding?– protocol of a systematic review and individual patient data meta-analysis.

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Word count 2550

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ABSTRACT

Introduction In order to reduce the risk of bleeding in patients on $P2Y_{12}$ receptor inhibitors presenting for non-emergent coronary artery bypass grafting (CABG), current guidelines recommend a preoperative discontinuation period of at least three, five and seven days for ticagrelor, clopidogrel, and prasugrel, respectively, to allow for recovery of platelet function. However, there is still substantial inter-institutional variation in preoperative management and relevant covariates of CABG-related bleeding are largely elusive so far.

Methods and analysis We will search PubMed (July 2013 to November 2021) and EMBASE (January 2014 to November 2021) using the following terms, MeSH terms and their synonyms: clopidogrel, prasugrel, ticagrelor, dual antiplatelet, $P2Y_{12}$ receptor inhibitor, CABG, bleeding, haemorrhage. Two independent reviewers will screen all abstracts and full papers for eligibility. Disagreements will be solved by consulting with a third reviewer.

The primary outcome is the incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding depending on type of $P2Y_{12}$ receptor inhibitor and preoperative withdrawal period. The secondary outcomes are mortality and myocardial infarction. We will perform an individual patient data meta-analysis (IPD-MA) with drug-specific preoperative withdrawal time and adjust for demographic and procedural variables. Subgroup analyses will be performed for anaemic patients and patients undergoing non-emergent versus urgent/emergent surgery.

Ethics and dissemination

This IPD-MA consists of secondary analyses of existing non-identifiable data and meets the criteria for waiver of ethics review by the local Research Ethics Committee. Data sharing and transfer will be subject to a confidentiality agreement and a data use

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agreement. Findings will be disseminated through peer-reviewed publication and

conference presentation.

PROSPERO registration number: CRD42022291946

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Strengths and Limitations

- In patients undergoing coronary artery bypass grafting (CABG) on $P2Y_{12}$ receptor inhibitors an individual patient data meta-analysis (IPD-MA) can be a superior method to standard meta-analysis, as it allows us to identify clinical and procedural variables potentially associated with surgery-related bleeding in addition to drug-specific preoperative withdrawal time.

- This IPD-MA sets out to evaluate the association between the drug-specific preoperative withdrawal time of $P2Y_{12}$ receptor inhibitors and the incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding, a "standardized" bleeding definition for patients on antithrombotic therapy.

- If we cannot get individual patient data for all identified studies, the risk of availability bias will be assessed by comparing study characteristics of those providing data and those that do not, and we will perform a sensitivity analysis.

- It is possible that in some studies not all information to calculate BARC-4 bleeding and the exact preoperative drug withdrawal period will be available but every attempt will be made to obtain these data.

- This IPD-MA will not be able to delineate a potential additional impact of anticoagulant agents on the incidence of BARC-4 bleeding.

BACKGROUND

In the 54 European Society of Cardiology (ESC) member countries 34.9 million people lived with ischemic heart disease in 2017. The median age-standardized prevalence per 1,000,000 inhabitants of each member country was 2270 (IQR 1508-2565) and was lower for females compared with males. In the 2018/19 survey, these figures translated into a median of 2047 (IQR 1478-2588) percutaneous coronary interventions and 301.1 (IQR 245.0-440.0) coronary artery bypass grafting operations (CABGs) per one million inhabitants.[1]

Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ receptor inhibitor on top of aspirin is the cornerstone to prevent thrombotic complications in patients with acute coronary syndromes (ACS) and/or after percutaneous coronary interventions with stents, albeit at the risk of increased bleeding.[2][3][4][5]

Large observational studies have demonstrated an association between the severity of cardiac surgery-related bleeding and 30-day postoperative morbidity and mortality.[6-10] A sub-study of the Transfusion Avoidance in Cardiac Surgery study (TACS) demonstrated that two consensus-based scoring systems for assessing the severity of bleeding, the Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery (UDPB) and the European Coronary Artery Bypass Graft (E-CABG), performed well in predicting 28-day mortality. Specifically, severe bleeding defined as either UDPB class 3 or E-CABG grade 2, both of which comprise transfusion of ≥ 5 units of red blood cells, was associated with about 40% relative increased risk of mortality.[6] Suggested mechanisms for bleeding-associated mortality are organ dysfunctions triggered by decreased oxygen delivery and hypotension following major blood loss in patients with atherosclerotic disease and adverse effects of transfusion.[11][12] Preventing perioperative blood loss may be more efficacious in improving outcome than mere reduction of allogenic blood components.[7]

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Currently, almost 11% of patients presenting with ACS have to undergo aorto-coronary bypass grafting during DAPT.[13]

In order to reduce the risk of bleeding in patients on $P2Y_{12}$ receptor inhibitors presenting for non-emergent cardiac surgery, current European Society of Cardiologist (ESC) and American Heart Association / American College of Cardiology (AHA / ACC) guidelines recommend a "standardized" preoperative discontinuation period of at least three days for ticagrelor, five days for clopidogrel, and seven days for prasugrel (II a recommendation) to allow for recovery of platelet function.[2 14 15] However, there is still substantial inter-institutional variation in preoperative management of ACS patients on DAPT, and there is heterogeneity in the definition and incidence of bleeding. Moreover, data on prasugrel are sparse.[7 16]

Two big registries used different bleeding definitions to evaluate the overall incidence of major CABG-related bleeding in patients on clopidogrel as compared to ticagrelor and the specific impact of preoperative withdrawal time.[8 9] The Swedish registry including 2,244 patients with ACS who underwent CABG demonstrated a 5% lower incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding in patients on ticagrelor as compared to clopidogrel (12.9% vs 17.6%, p=0.033). This difference was mainly driven by a sharp decline in bleeding after 72 hours withdrawal of ticagrelor as compared to a more gradual decrease with clopidogrel. Importantly, incidence of BARC-4 bleeding was 38 and 31% when ticagrelor / clopidogrel was discontinued less than 24 hours, preoperatively.[8] In contrast, a subgroup analysis of 1,376 patients from the E-CABG registry demonstrated a similar incidence of severe or massive UDPB (11.2% vs 8.7%, p=0.14) and BARC-4 bleeding (13.2% vs 11.6%, p=0.38) in clopidogrel and ticagrelor treated patients, and a similar decrease in bleeding with increasing days off $P2Y_{12}$ receptor inhibitors, compatible with time-dependent recovery of platelet function. In a propensity score-matched analysis, 4 to 5 days off clopidogrel reduced severe /

massive UDPB class by 7.3% as compared to a 3 days preoperative withdrawal period (p=0.031). Similarly, 3 days off ticagrelor reduced bleeding by 13.3% as compared to a 0-2 days preoperative withdrawal period (p=0.003).[9]

However, the additional impact of covariates known to affect CABG-related bleeding, the potential bias introduced by preoperative anaemia, occurring in up to 40% of patients undergoing cardiac surgery, and the incidence of myocardial infarction in this particular patient population remain largely elusive so far.[17-21]

The proposed review is therefore needed to determine the effect of preoperative $P2Y_{12}$ receptor inhibitors and time of preoperative withdrawal in patients undergoing on-pump CABG on primary (BARC-4 bleeding) and secondary outcomes (all-cause mortality and myocardial infarction) in studies published from July 2013 to November 2021. Studies published until June 2013 have been included in a prior pooled meta-analysis which demonstrated that late preoperative discontinuation of $P2Y_{12}$ receptor inhibitors (< 5 days) was associated with a 2.5- and 1.5- fold increased risk of reoperation for bleeding and death, respectively, as compared to early (≥ 5 days) preoperative discontinuation.[21]

Although not yet validated regarding the risk of CABG-associated morbidity and mortality, we decided to use the BARC-4 bleeding definition because BARC bleeding has been introduced as a standardized bleeding endpoint for patients receiving antithrombotic therapy.[22]

To fill the gaps in the knowledge as outlined above we will aim to conduct an individual patient data meta-analysis (IPD-MA). The primary objective will be to assess the incidence of BARC-4 bleeding depending on type of $P2Y_{12}$ receptor inhibitors and drug-specific preoperative withdrawal period. Furthermore, the effect of preoperative $P2Y_{12}$ receptor inhibitors on in-hospital / 30-day all-cause mortality and myocardial infarction in on-pump CABG patients will be evaluated. We will correct for demographic and procedural variables and we will perform subgroup analyses to identify the influence of

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preoperative anaemia and non-emergent CABG vs urgent / emergent CABG on outcome.

METHODS AND ANALYSES

This IPD-MA protocol is registered on PROSPERO. The review will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) Statement[23]

Sources of evidence and search strategy

We will search PubMed (July 2013 to November 2021, search strategy see table 1) and EMBASE (2014 to 2021, search strategy see table 2) for a combination of terms, MeSH terms and their synonyms in titles and abstracts like 'clopidogrel', 'prasugrel', 'ticagrelor', 'dual antiplatelet', 'P2Y$_{12}$ receptor inhibitor', 'CABG', 'bleeding', 'haemorrhage'. Vocabulary and syntax will be adjusted across databases. This strategy was reviewed by a librarian of the Medical University of Graz (AS). Two researchers (IL, MS) will search separately according to the search strategy as described in table 1 and 2. We will also search the Cochrane Library and will carry out a hand search. Unpublished ongoing clinical studies will be searched from WHO International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov and Prospero (until November 2021).

Table 1 Search strategy for PubMed	
ID	Query
#1	(clopidogrel OR Prasugrel OR Ticagrelor OR dual antiplatelet OR dual-antiplatelet OR P2Y12 receptor inhibitor OR p2y12 receptor antagonist OR p2y12 Inhibitor OR p2y12-inhibitor OR P2Y12 inhibit* OR P2Y12-Inhibit* OR platelet aggregation inhibitor* OR thienopyridine OR ADP receptor blocking agent OR ADP receptor antagonist OR ADP-receptor antagonist OR Adenosine diphosphate receptor antagonist OR ADP-Receptor* OR ADP Receptor* OR Purinergic P2Y Receptor Antagonists [MeSH])

#2	(cabg OR cardiac surgery OR coronary artery bypass OR Coronary artery surgery OR coronary surgery OR Coronary bypass surgery OR heart surgery OR "on pump" OR on-pump OR Coronary revascularization OR Coronary revascularisation OR myocardial revascularization OR myocardial revascularisation OR ((coronary OR cardiac) AND (bypass OR surgery OR surgical OR operation OR operative)) OR Coronary Artery Bypass [MeSH] OR myocardial revascularization [MeSH])
#3	(bleeding OR bleed* OR hemorrhage OR hemorrhag* OR haemorrhage OR haemorrhag* OR barc OR Blood loss OR Blood Loss, Surgical [MeSH] OR hemorrhage [MeSH Terms])
#4	#1 AND #2 AND #3
#5	#4 AND July 2013 - November 2021
#6	#5 AND English

Table 2 Search strategy for Embase	
ID	**Query**
#1	clopidogrel OR Prasugrel OR Ticagrelor OR dual antiplatelet* OR dual-antiplatelet* OR P2Y12 receptor inhibitor OR p2y12 receptor antagonist OR p2y12 Inhibitor OR p2y12-inhibitor OR P2Y12 inhibit* OR P2Y12-Inhibit* OR platelet aggregation inhibitor* OR thienopyridine* OR ADP receptor blocking agent* OR ADP receptor antagonist* OR ADP-receptor antagonist* OR Adenosine diphosphate receptor antagonist OR ADP-Receptor* OR ADP Receptor*
#2	cabg OR cardia* surg* OR coronary artery bypass OR Coronary artery surg* OR coronar* surg* OR Coronary bypass surg* OR heart surg* OR on pump OR on-pump OR Coronar* revasculari* OR myocardial revasculari*
#3	bleed* OR hemorrhag* OR haemorrhag* OR barc OR Blood los*
#4	Blood adj3 los
#5	#3 OR #4
#6	#1 AND #2 AND #5
#7	#6 AND English language
#8	#7 AND 2014 – current

Inclusion and exclusion criteria

We will include randomized controlled trials (RCTs) and observational trials that evaluate

the effect of different P2Y$_{12}$ receptor inhibitors (clopidogrel, prasugrel and ticagrelor) and

drug-free period prior to surgery on any of the defined outcome measures (BARC-4

bleeding, mortality, non-fatal myocardial infarction), to assess differences depending on

1. the individual P2Y$_{12}$ receptor inhibitor and

2. preoperative withdrawal time.

We will include adult female and male patients of any age undergoing on-pump CABG during dual antiplatelet therapy with aspirin and a P2Y$_{12}$ receptor inhibitor

Inclusion criteria are:

- full text articles in English

- Isolated on-pump CABG

- Patients on DAPT (irrespective of type of P2Y$_{12}$ inhibitor) with the withdrawal period being equal to or shorter than 7 days

- At least one BARC-4 criteria documented

Exclusion criteria are:

- Off-pump CABG

- Complex surgery (e.g., CABG + valve)

- Timing of surgery based on preoperative platelet function

Intervention

Intervention: CABG with a drug-specific preoperative withdrawal time of P2Y$_{12}$ receptor inhibitors (clopidogrel, prasugrel or ticagrelor) shorter than suggested by ESC and AHA / ACC guidelines.

Comparison: CABG with a drug-specific preoperative withdrawal period of P2Y$_{12}$ receptor inhibitors (clopidogrel, prasugrel or ticagrelor) according to the ESC and AHA / ACC guidelines.

Outcomes

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Primary outcome

- BARC-4 bleeding, defined as any of the following:[22]

  a) perioperative intracranial bleeding within 48 hours,

  b) reoperation after closure of sternotomy for the purpose of controlling bleeding,

  c) transfusion of 5 units or more of packed RBCs within 48 hours, or

  d) 24-hour chest tube drainage of 2000 mL or more

Secondary outcomes

- Mortality (in-hospital mortality / 30-day mortality)

- Non-fatal myocardial infarction according to the 4th universal definition of MI and

to definitions used in studies included in this meta-analysis.[24]

Languages

English

Time

Study start 04 2021; anticipated study end 03/2023

Study records

Data management

All search results will be downloaded into a compatible version of MS Excel (MS Office Professional Plus 2016) from the interfaces. We will transfer these results into a common Excel file for deduplication. For manual deduplication we will have two criteria, title and author, to unambiguously recognize duplicates. Finally, we will do a cross check of the number of included studies.

Selection process

Using the results of the above searches, two authors (IL and MS) will independently screen all titles and abstracts for eligibility. Each of the two authors will document the reason for exclusion of each trial to be excluded. All records deemed potentially relevant by at least one author will be obtained in full text format and assessed according to eligibility criteria independently by IL and MS. In a second step, these evaluations will be discussed with a third researcher (EM) to resolve disagreements. The selection process will be plotted in a flow diagram in accordance with the PRISMA-P statement (figure 1). [23 25]

Data extraction and management

We will independently extract study characteristics such as study design (RCTs, observational trials), authors, year of publication and setting of study. We will aim to perform an IPD-MA for the review questions because the main outcome of interest, BARC-4 bleeding, is not generally reported in the literature. IPD-MA would furthermore allow for the direct incorporation of demographic and procedural variables that were previously identified as potential confounders of increased bleeding into the analysis. [7 16 26]

Following the selection process, we will address the first author or, if unavailable, the corresponding author of each identified study. All authors will be asked to provide a selection of parameters from their original datasets in a pseudonymized fashion that does not allow identification of individual identities. We will provide an Excel sheet outlining the requested parameters (see table 3). After accepting the invitation to collaborate and signing both a confidentiality and data transfer agreement, the authors will be asked to share their data via a secure server of the Medical University of Graz.

This uploading process is encrypted. The stored data will be protected by access authorisation. The received data will be reviewed to assess the completeness and accuracy of the dataset.

Table 3 Parameters requested from individual studies

	Parameter	Categories/Unit
demographics	Age[1]	years
	Gender[1]	m/f
	Weight	Kg
	Height	M
	BMI	kg/m²
	Creatinine	mg/dl or µmol/l
	Creatinine clearance[1]	ml/min
	Diabetes mellitus	y/n
	Liver disease	y/n
	LVEF[1]	%
	Euroscore 2	
	UFH or LMWH or fondaparinux (within 24 hours preop)	y/n
Procedural variables	Urgency[1]	Elective/urgent/emergency/salvage
	CABG indication	Stable CAD/NSTEMI/STEMI
	CPB time	minutes
	Number of arterial grafts	
	Number of distal anastomoses	
	Tranexamic acid during surgery	y/n
	Hb preoperative	g/l
	Platelets preoperative	x10⁹/l
	Institutional protocol for treating postpump bleeding	y/n
	ASS perioperative continuation	y/n
	ASS cessation prior to surgery	days
	Clopidogrel preoperative	y/n
	Clopidogrel cessation prior to surgery	days
	Prasugrel preoperative	y/n
	Prasugrel cessation prior to surgery	days
	Ticagrelor preoperative	y/n
	Ticagrelor cessation prior to surgery	days
outcome	Chest tube drainage volume within 24h[2]	ml
	Reoperation due to bleeding	y/n
	Intracranial bleeding within 48h hours perioperatively	y/n
	Number of transfused red blood	

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cell units within 48 Hours from incision	
Postoperative MI	y/n
In hospital mortality	y/n
30 day mortality	y/n

*Calculated parameter, [1]part of euroscore II, [2]if unavailable chest tube drainage volume obtained during shorter observation period (define observation period)

Plausibility checks of the received data will be performed by comparing summary measures of the IPD with the published data as well as by checking plausibility of the individual values in a clinical context. Any implausibilities will be resolved with the original authors through queries. Individual datasets will be pre-processed and merged into a single datafile for analysis. At the end of the study all original individual datasets will be deleted.

Risk of bias

Two authors (IL, MS) will assess the risk of bias for each trial independently. Possible disagreements will be resolved by consensus, or with consultation of a third party (EM). For RCTs, we will assess risk of bias using the Cochrane Collaboration's tool.[27] We will use the following bias criteria:

- random sequence generation (selection bias),

- allocation concealment (selection bias),

- blinding (performance bias and detection bias), separately for blinding of participants and personnel and blinding of outcome assessment,

- incomplete outcome data (attrition bias),

- selective reporting (reporting bias),

- other bias.

We will judge risk of bias criteria as 'low risk', 'high risk' or 'unclear risk' as described in the Cochrane Handbook for Systematic Reviews of Interventions.[27]

For observational studies, the quality of each study will be assessed using the Robins-I Tool as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[27]

The following domains will be assessed:

- bias due to confounding,

- bias in selection of participants into the study,

- bias in classification of interventions,

- bias due to deviations from intended interventions,

- bias due to missing data,

- bias in measurement of outcomes,

- bias in selection of the reported result.

Data synthesis

The primary analysis will be performed as a two-stage IPD-MA. For this approach, each study will first be individually analysed according to a pre-specified regression model for each type of $P2Y_{12}$ inhibitor including drug specific preoperative withdrawal time as well as relevant confounders (see table 3). The results of these analyses will be presented as odds ratios (OR) and 95% confidence intervals (CI) and can be displayed in a forest plot. For the second stage, these results will be pooled using standard meta-analytic methods, in our case random-effects models.

If we cannot get individual patient data for all identified studies, the risk of availability bias will be assessed by comparing study characteristics of those providing data and those that do not. For studies not providing individual patient data but presenting the

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respective outcomes, we will incorporate these results in a sensitivity analysis to test the robustness of the IPD findings. Furthermore, the equivalent to the well-known Funnel plot can be visually assessed.

Additionally, subgroup analyses are planned for:

- patients undergoing non-emergent CABG vs patients undergoing urgent / emergent CABG because of ACS and

- patients preoperatively presenting with anaemia according to the World Health Organization-definition of less than 13 g/dL for men and less than 12 g/dL for women vs preoperatively non-anaemic patients.

Furthermore, sensitivity analyses will test the robustness of our findings for the analysis of the primary outcome. They will be performed for study quality and drug-specific preoperative withdrawal periods for each single day of withdrawal, including no preoperative withdrawal.

The analyses will be performed using a current version of R. No imputation for missing data is planned. The analyses are performed in accordance with the handbook of the Cochrane collaboration and results will be presented according to the PRISMA-IPD statement. [23]

Legend to figure 1 Flow chart diagram presenting the selection of articles for systemic review and meta-analysis of incidence of BARC-4 bleeding depending on type of $P2Y_{12}$ receptor inhibitor and preoperative withdrawal period.

Ethics and dissemination

This IPD-MA consists of secondary analyses of existing non-identifiable data and meets the criteria for waiver of ethics review by the local Research Ethics Committee. Data sharing and transfer will be subject to a confidentiality agreement and a data use agreement. Findings will be disseminated through peer-reviewed publication and conference presentation.

Contributors

Schoerghuber: study design, bibliographic research, design of data entry forms, data management, conduct of study, protocol and manuscript writing

Pregartner: study design, data management, statistical analysis, protocol and manuscript writing and review

Berghold: study design, data management, study design, data management, statistical analysis, protocol and manuscript review

Lindenau: bibliographic research, design of data entry forms, data management, conduct of study, protocol and manuscript review

Zweiker: Scientific coordination, protocol and manuscript writing and review

Voetsch: Scientific coordination, protocol and manuscript review

Mahla: study design, scientific coordination, protocol and manuscript writing and review

Zirlik: Scientific coordination, protocol and manuscript review

Funding

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Competing interests

Michael Schoerghuber no conflicts of interest

Gudrun Pregartner no conflicts of interest

Andrea Berghold no conflicts of interest

Ines Lindenau no conflicts of interest

Robert Zweiker no conflicts of interest

Andreas Voetsch no conflicts of interest

Elisabeth Mahla no conflicts of interest

Andreas Zirlik received honoraria for lectures and consulting of Daiichi Sankyo, Lilly,

AstraZeneca, Bristol Myers Squibb, Pfizer, Bayer, Boehringer Ingelheim

Patient and public involvement

Patients and / or the public were not involved in the design, conduct, reporting or

dissemination plans of this research

Patient consent for publication

Not applicable

Provenance and peer review

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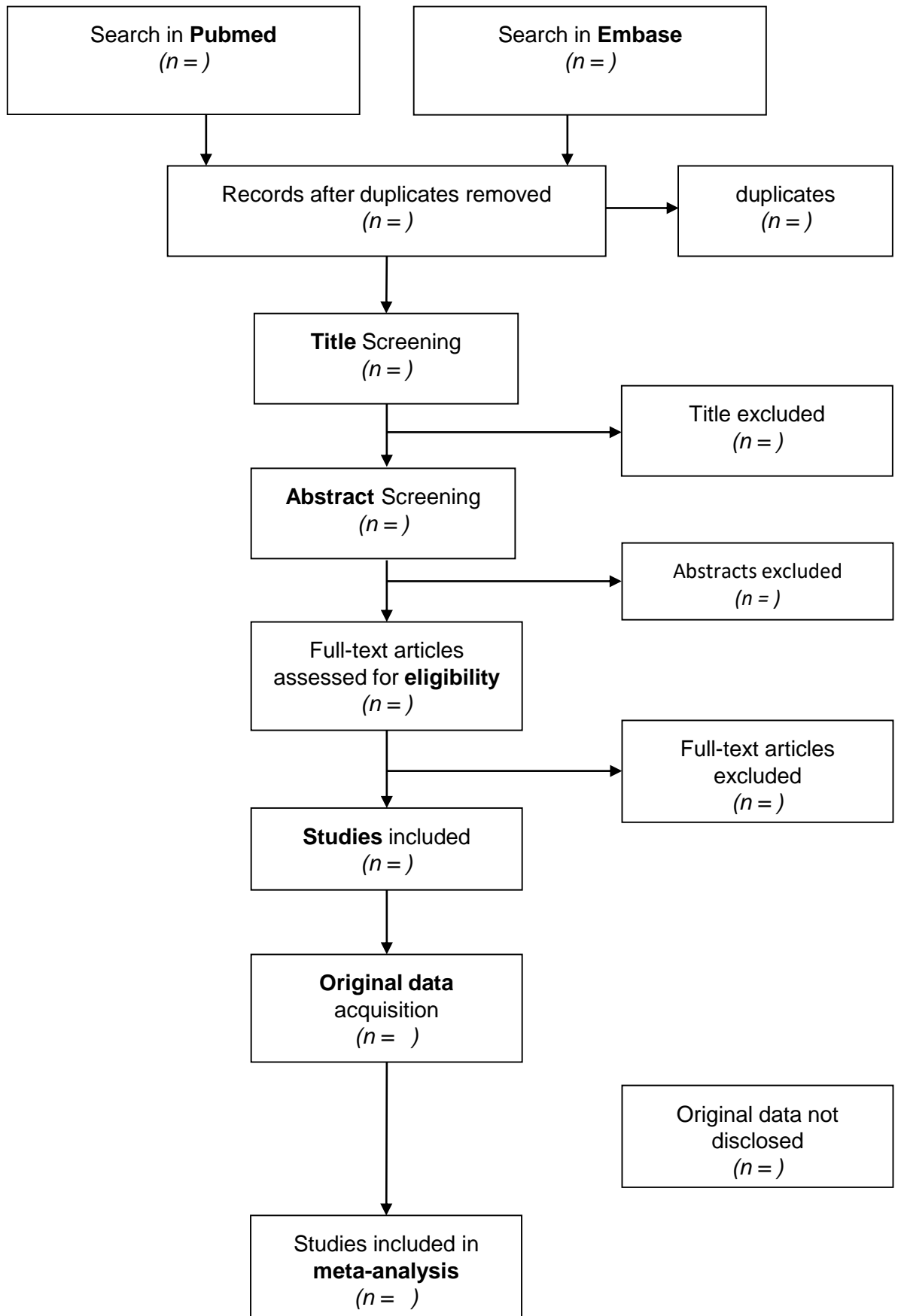
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Identification

Search in **Pubmed**
(n =)

Search in **Embase**
(n =)

Records after duplicates removed
(n =)

duplicates
(n =)

Screening

Title Screening
(n =)

Title excluded
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Abstract Screening
(n =)

Abstracts excluded
(n =)

Eligibility

Full-text articles
assessed for **eligibility**
(n =)

Full-text articles
excluded
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Included

Studies included
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Original data
acquisition
(n =   )

Original data not
disclosed
(n =)

Studies included in
meta-analysis
(n =   )

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	17
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8-9
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-14
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	13-14

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	13-14
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	14-15
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2 , Kendall's τ)	15-16
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6-7

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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How do type of preoperative P2Y12 receptor inhibitor and withdrawal time affect bleeding? – protocol of a systematic review and individual patient data meta-analysis.

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How do type of preoperative P2Y₁₂ receptor inhibitor and withdrawal time affect bleeding?– protocol of a systematic review and individual patient data meta-analysis.

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Word count 2686

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ABSTRACT

Introduction In order to reduce the risk of bleeding in patients on P2Y$_{12}$ receptor inhibitors presenting for non-emergent coronary artery bypass grafting (CABG), current guidelines recommend a preoperative discontinuation period of at least three, five and seven days for ticagrelor, clopidogrel, and prasugrel, respectively, to allow for recovery of platelet function. However, there is still substantial inter-institutional variation in preoperative management and relevant covariates of CABG-related bleeding are largely elusive so far.

Methods and analysis We will search PubMed (July 2013 to November 2021) and EMBASE (January 2014 to November 2021) using the following terms, MeSH terms and their synonyms: clopidogrel, prasugrel, ticagrelor, dual antiplatelet, P2Y$_{12}$ receptor inhibitor, CABG, bleeding, haemorrhage. Two independent reviewers will screen all abstracts and full papers for eligibility. Disagreements will be solved by consulting with a third reviewer.

The primary outcome is the incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding depending on type of P2Y$_{12}$ receptor inhibitor and preoperative withdrawal period. The secondary outcomes are mortality and ischemic events according to the Academic Research Consortium 2 Consensus Document. We will perform an individual patient data meta-analysis (IPD-MA) with drug-specific preoperative withdrawal time and adjust for demographic and procedural variables. Subgroup analyses will be performed for anaemic patients and patients undergoing non-emergent versus urgent/emergent surgery.

Ethics and dissemination

This IPD-MA consists of secondary analyses of existing non-identifiable data and meets the criteria for waiver of ethics review by the local Research Ethics Committee. Data

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sharing and transfer will be subject to a confidentiality agreement and a data use

agreement. Findings will be disseminated through peer-reviewed publication and

conference presentation.

PROSPERO registration number: CRD42022291946

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Strengths and Limitations

- In patients undergoing coronary artery bypass grafting (CABG) on P2Y$_{12}$ receptor inhibitors an individual patient data meta-analysis (IPD-MA) can be a superior method to standard meta-analysis, as it allows us to identify clinical and procedural variables potentially associated with surgery-related bleeding in addition to drug-specific preoperative withdrawal time.

- This IPD-MA sets out to evaluate the association between the drug-specific preoperative withdrawal time of P2Y$_{12}$ receptor inhibitors and the incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding, a "standardized" bleeding definition for patients on antithrombotic therapy and potential tradeoffs in terms of ischemic events comprising death, myocardial infarction, and stent thrombosis according to Academic Research Consortium 2 Consensus Document.

- If we cannot get individual patient data for all identified studies, the risk of availability bias will be assessed by comparing study characteristics of those providing data and those that do not, and we will perform a sensitivity analysis.

- It is possible that in some studies not all information to calculate BARC-4 bleeding and the exact preoperative drug withdrawal period will be available but every attempt will be made to obtain these data.

- This IPD-MA will not be able to delineate a potential additional impact of anticoagulant agents on the incidence of BARC-4 bleeding.

BACKGROUND

In the 54 European Society of Cardiology (ESC) member countries 34.9 million people lived with ischemic heart disease in 2017. The median age-standardized prevalence per 1,000,000 inhabitants of each member country was 2270 (IQR 1508-2565) and was lower for females compared with males. In the 2018/19 survey, these figures translated into a median of 2047 (IQR 1478-2588) percutaneous coronary interventions and 301.1 (IQR 245.0-440.0) coronary artery bypass grafting operations (CABGs) per one million inhabitants.[1]

Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ receptor inhibitor on top of aspirin is the cornerstone to prevent thrombotic complications in patients with acute coronary syndromes (ACS) and/or after percutaneous coronary interventions with stents, albeit at the risk of increased bleeding.[2][3][4][5]

Large observational studies have demonstrated an association between the severity of cardiac surgery-related bleeding and 30-day postoperative morbidity and mortality.[6-10] A sub-study of the Transfusion Avoidance in Cardiac Surgery study (TACS) demonstrated that two consensus-based scoring systems for assessing the severity of bleeding, the Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery (UDPB) and the European Coronary Artery Bypass Graft (E-CABG), performed well in predicting 28-day mortality. Specifically, severe bleeding defined as either UDPB class 3 or E-CABG grade 2, both of which comprise transfusion of ≥ 5 units of red blood cells, was associated with about 40% relative increased risk of mortality.[6] Suggested mechanisms for bleeding-associated mortality are organ dysfunctions triggered by decreased oxygen delivery and hypotension following major blood loss in patients with atherosclerotic disease and adverse effects of transfusion.[11][12] Preventing perioperative blood loss may be more efficacious in improving outcome than mere reduction of allogenic blood components.[7]

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Currently, almost 11% of patients presenting with ACS have to undergo aorto-coronary bypass grafting during DAPT.[13]

In order to reduce the risk of bleeding in patients on $P2Y_{12}$ receptor inhibitors presenting for non-emergent cardiac surgery, current European Society of Cardiologist (ESC) and American Heart Association / American College of Cardiology (AHA / ACC) guidelines recommend a "standardized" preoperative discontinuation period of at least three days for ticagrelor, five days for clopidogrel, and seven days for prasugrel (II a recommendation) to allow for recovery of platelet function.[2 14 15] However, there is still substantial inter-institutional variation in preoperative management of ACS patients on DAPT, and there is heterogeneity in the definition and incidence of bleeding. Moreover, data on prasugrel are sparse. [7 16]

Two big registries used different bleeding definitions to evaluate the overall incidence of major CABG-related bleeding in patients on clopidogrel as compared to ticagrelor and the specific impact of preoperative withdrawal time.[8 9] The Swedish registry including 2,244 patients with ACS who underwent CABG demonstrated a 5% lower incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding in patients on ticagrelor as compared to clopidogrel (12.9% vs 17.6%, p=0.033). This difference was mainly driven by a sharp decline in bleeding after 72 hours withdrawal of ticagrelor as compared to a more gradual decrease with clopidogrel. Importantly, incidence of BARC-4 bleeding was 38 and 31% when ticagrelor / clopidogrel was discontinued less than 24 hours, preoperatively.[8] In contrast, a subgroup analysis of 1,376 patients from the E-CABG registry demonstrated a similar incidence of severe or massive UDPB (11.2% vs 8.7%, p=0.14) and BARC-4 bleeding (13.2% vs 11.6%, p=0.38) in clopidogrel and ticagrelor treated patients, and a similar decrease in bleeding with increasing days off $P2Y_{12}$ receptor inhibitors, compatible with time-dependent recovery of platelet function. In a propensity score-matched analysis, 4 to 5 days off clopidogrel reduced severe /

massive UDPB class by 7.3% as compared to a 3 days preoperative withdrawal period (p=0.031). Similarly, 3 days off ticagrelor reduced bleeding by 13.3% as compared to a 0-2 days preoperative withdrawal period (p=0.003).[9]

However, the additional impact of covariates known to affect CABG-related bleeding, the potential bias introduced by preoperative anaemia, occurring in up to 40% of patients undergoing cardiac surgery, and the incidence of myocardial infarction in this particular patient population remain largely elusive so far.[17-21]

The proposed review is therefore needed to determine the effect of preoperative $P2Y_{12}$ receptor inhibitors and time of preoperative withdrawal in patients undergoing on-pump CABG on primary (BARC-4 bleeding) and secondary outcomes (all-cause mortality and myocardial infarction) in studies published from July 2013 to November 2021. Studies published until June 2013 have been included in a prior pooled meta-analysis which demonstrated that late preoperative discontinuation of $P2Y_{12}$ receptor inhibitors (< 5 days) was associated with a 2.5- and 1.5- fold increased risk of reoperation for bleeding and death, respectively, as compared to early (≥ 5 days) preoperative discontinuation.[21]

Although not yet validated regarding the risk of CABG-associated morbidity and mortality, we decided to use the BARC-4 bleeding definition because BARC bleeding has been introduced as a standardized bleeding endpoint for patients receiving antithrombotic therapy.[22]

To fill the gaps in the knowledge as outlined above we will aim to conduct an individual patient data meta-analysis (IPD-MA). The primary objective will be to assess the incidence of BARC-4 bleeding depending on type of $P2Y_{12}$ receptor inhibitors and drug-specific preoperative withdrawal period. Furthermore, the effect of preoperative $P2Y_{12}$ receptor inhibitors on in-hospital / 30-day all-cause mortality and myocardial infarction in on-pump CABG patients will be evaluated. We will correct for demographic and procedural variables and we will perform subgroup analyses to identify the influence of

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preoperative anaemia and non-emergent CABG vs urgent / emergent CABG on outcome.

METHODS AND ANALYSES

This IPD-MA protocol is registered on PROSPERO. The review will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) Statement[23]

Sources of evidence and search strategy

We will search PubMed (July 2013 to November 2021, search strategy see table 1) and EMBASE (2014 to 2021, search strategy see table 2) for a combination of terms, MeSH terms and their synonyms in titles and abstracts like 'clopidogrel', 'prasugrel', 'ticagrelor', 'dual antiplatelet', 'P2Y$_{12}$ receptor inhibitor', 'CABG', 'bleeding', 'haemorrhage'. Vocabulary and syntax will be adjusted across databases. This strategy was reviewed by a librarian of the Medical University of Graz (AS). Two researchers (IL, MS) will search separately according to the search strategy as described in table 1 and 2. We will also search the Cochrane Library and will carry out a hand search. Unpublished ongoing clinical studies will be searched from WHO International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov and Prospero (until November 2021).

Table 1 Search strategy for PubMed	
ID	**Query**
#1	(clopidogrel OR Prasugrel OR Ticagrelor OR dual antiplatelet OR dual-antiplatelet OR P2Y12 receptor inhibitor OR p2y12 receptor antagonist OR p2y12 Inhibitor OR p2y12-inhibitor OR P2Y12 inhibit* OR P2Y12-Inhibit* OR platelet aggregation inhibitor* OR thienopyridine OR ADP receptor blocking agent OR ADP receptor antagonist OR ADP-receptor antagonist OR Adenosine diphosphate receptor antagonist OR ADP-Receptor* OR ADP Receptor* OR Purinergic P2Y Receptor Antagonists [MeSH])

#2	(cabg OR cardiac surgery OR coronary artery bypass OR Coronary artery surgery OR coronary surgery OR Coronary bypass surgery OR heart surgery OR "on pump" OR on-pump OR Coronary revascularization OR Coronary revascularisation OR myocardial revascularization OR myocardial revascularisation OR ((coronary OR cardiac) AND (bypass OR surgery OR surgical OR operation OR operative)) OR Coronary Artery Bypass [MeSH] OR myocardial revascularization [MeSH])
#3	(bleeding OR bleed* OR hemorrhage OR hemorrhag* OR haemorrhage OR haemorrhag* OR barc OR Blood loss OR Blood Loss, Surgical [MeSH] OR hemorrhage [MeSH Terms])
#4	#1 AND #2 AND #3
#5	#4 AND July 2013 - November 2021
#6	#5 AND English

Table 2 Search strategy for Embase	
ID	Query
#1	clopidogrel OR Prasugrel OR Ticagrelor OR dual antiplatelet* OR dual-antiplatelet* OR P2Y12 receptor inhibitor OR p2y12 receptor antagonist OR p2y12 Inhibitor OR p2y12-inhibitor OR P2Y12 inhibit* OR P2Y12-Inhibit* OR platelet aggregation inhibitor* OR thienopyridine* OR ADP receptor blocking agent* OR ADP receptor antagonist* OR ADP-receptor antagonist* OR Adenosine diphosphate receptor antagonist OR ADP-Receptor* OR ADP Receptor*
#2	cabg OR cardia* surg* OR coronary artery bypass OR Coronary artery surg* OR coronar* surg* OR Coronary bypass surg* OR heart surg* OR on pump OR on-pump OR Coronar* revasculari* OR myocardial revasculari*
#3	bleed* OR hemorrhag* OR haemorrhag* OR barc OR Blood los*
#4	Blood adj3 los
#5	#3 OR #4
#6	#1 AND #2 AND #5
#7	#6 AND English language
#8	#7 AND 2014 – current

Inclusion and exclusion criteria

We will include randomized controlled trials (RCTs) and observational trials that evaluate

the effect of different P2Y$_{12}$ receptor inhibitors (clopidogrel, prasugrel and ticagrelor) and

drug-free period prior to surgery on any of the defined outcome measures (BARC-4

bleeding, mortality, non-fatal myocardial infarction), to assess differences depending on

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1. the individual $P2Y_{12}$ receptor inhibitor and

2. preoperative withdrawal time.

We will include adult female and male patients of any age undergoing on-pump CABG during dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor

Inclusion criteria are:

- full text articles in English

- Isolated on-pump CABG

- Patients on DAPT (irrespective of type of $P2Y_{12}$ inhibitor) with the withdrawal period being equal to or shorter than 7 days

- At least one BARC-4 criteria documented

Exclusion criteria are:

- Off-pump CABG

- Complex surgery (e.g., CABG + valve)

- Timing of surgery based on preoperative platelet function

Intervention

Intervention: CABG with a drug-specific preoperative withdrawal time of $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel or ticagrelor) shorter than suggested by ESC and AHA / ACC guidelines.

Comparison: CABG with a drug-specific preoperative withdrawal period of $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel or ticagrelor) according to the ESC and AHA / ACC guidelines.

Outcomes

Primary outcome

- BARC-4 bleeding, defined as any of the following:[22]

    a) perioperative intracranial bleeding within 48 hours,

    b) reoperation after closure of sternotomy for the purpose of controlling bleeding,

    c) transfusion of 5 units or more of packed RBCs within 48 hours, or

    d) 24-hour chest tube drainage of 2000 mL or more

Secondary outcomes

- Mortality (in-hospital mortality / 30-day mortality)

- Ischemic end points defined according to the Academic Research Consortium-2 Consensus Document comprising death, myocardial infarction, and stent thrombosis.[24]

Languages

English

Time

Study start 04 2021; anticipated study end 03/2023

Study records

Data management

All search results will be downloaded into a compatible version of MS Excel (MS Office Professional Plus 2016) from the interfaces. We will transfer these results into a common Excel file for deduplication. For manual deduplication we will have two criteria,

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title and author, to unambiguously recognize duplicates. Finally, we will do a cross check of the number of included studies.

Selection process

Using the results of the above searches, two authors (IL and MS) will independently screen all titles and abstracts for eligibility. Each of the two authors will document the reason for exclusion of each trial to be excluded. All records deemed potentially relevant by at least one author will be obtained in full text format and assessed according to eligibility criteria independently by IL and MS. In a second step, these evaluations will be discussed with a third researcher (EM) to resolve disagreements. The selection process will be plotted in a flow diagram in accordance with the PRISMA-P statement (figure 1). [23 25]

Data extraction and management

We will independently extract study characteristics such as study design (RCTs, observational trials), authors, year of publication and setting of study. We will aim to perform an IPD-MA for the review questions because the main outcome of interest, BARC-4 bleeding, is not generally reported in the literature. IPD-MA would furthermore allow for the direct incorporation of demographic and procedural variables that were previously identified as potential confounders of increased bleeding into the analysis. [7 16 26]

Following the selection process, we will address the first author or, if unavailable, the corresponding author of each identified study. All authors will be asked to provide a selection of parameters from their original datasets in a pseudonymized fashion that does not allow identification of individual identities. We will provide an Excel sheet outlining the requested parameters (see table 3). After accepting the invitation to

collaborate and signing both a confidentiality and data transfer agreement, the authors will be asked to share their data via a secure server of the Medical University of Graz. This uploading process is encrypted. The stored data will be protected by access authorisation. The received data will be reviewed to assess the completeness and accuracy of the dataset.

Table 3 Parameters requested from individual studies

	Parameter	Categories/Unit
demographics	Age[1]	Years
	Gender[1]	m/f
	Weight	Kg
	Height	M
	BMI	kg/m²
	Creatinine	mg/dl or µmol/l
	Creatinine clearance[1]	ml/min
	Diabetes mellitus	y/n
	Liver disease	y/n
	LVEF[1]	%
	Euroscore 2	
	UFH or LMWH or fondaparinux (within 24 hours preop)	y/n
Procedural variables	Urgency[1]	Elective/urgent/emergency/salvage
	CABG indication	Stable CAD/NSTEMI/STEMI
	CPB time	Minutes
	Number of arterial grafts	
	Number of distal anastomoses	
	Tranexamic acid during surgery	y/n
	Hb preoperative	g/l
	Platelets preoperative	x10⁹/l
	Institutional protocol for treating postpump bleeding	y/n
	ASS perioperative continuation	y/n
	ASS cessation prior to surgery	Days
	Clopidogrel preoperative	y/n
	Clopidogrel cessation prior to surgery	Days
	Prasugrel preoperative	y/n
	Prasugrel cessation prior to surgery	Days
	Ticagrelor preoperative	y/n
	Ticagrelor cessation prior to surgery	Days
outc	Chest tube drainage volume within 24h[2]	Ml

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Reoperation due to bleeding	y/n
Intracranial bleeding within 48h hours perioperatively	y/n
Number of transfused red blood cell units within 48 Hours from incision	
Postoperative MI	y/n
In hospital mortality	y/n
30 day mortality	y/n

*Calculated parameter, ¹part of euroscore II, ²if unavailable chest tube drainage volume obtained during shorter observation period (define observation period)

Plausibility checks of the received data will be performed by comparing summary

measures of the IPD with the published data as well as by checking plausibility of the

individual values in a clinical context. Any implausibilities will be resolved with the

original authors through queries. Individual datasets will be pre-processed and merged

into a single datafile for analysis. At the end of the study all original individual datasets

will be deleted.

Risk of bias

Two authors (IL, MS) will assess the risk of bias for each trial independently. Possible

disagreements will be resolved by consensus, or with consultation of a third party (EM).

For RCTs, we will assess risk of bias using the Cochrane Collaboration's tool.[27] We will

use the following bias criteria:

- random sequence generation (selection bias),

- allocation concealment (selection bias),

- blinding (performance bias and detection bias), separately for blinding of

  participants and personnel and blinding of outcome assessment,

- incomplete outcome data (attrition bias),

- selective reporting (reporting bias),

- other bias.

We will judge risk of bias criteria as 'low risk', 'high risk' or 'unclear risk' as described in the Cochrane Handbook for Systematic Reviews of Interventions.[27]

For observational studies, the quality of each study will be assessed using the Robins-I Tool as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[27]

The following domains will be assessed:

- bias due to confounding,

- bias in selection of participants into the study,

- bias in classification of interventions,

- bias due to deviations from intended interventions,

- bias due to missing data,

- bias in measurement of outcomes,

- bias in selection of the reported result.

Data synthesis

The primary analysis will be performed as a two-stage IPD-MA. For this approach, each study will first be individually analysed according to a pre-specified regression model for each type of $P2Y_{12}$ inhibitor including drug specific preoperative withdrawal time as well as relevant confounders (see table 3). The results of these analyses will be presented as odds ratios (OR) and 95% confidence intervals (CI) and can be displayed in a forest plot. For the second stage, these results will be pooled using standard meta-analytic methods, in our case random-effects models.

If we cannot get individual patient data for all identified studies, the risk of availability bias will be assessed by comparing study characteristics of those providing data and

those that do not. For studies not providing individual patient data but presenting the respective outcomes, we will incorporate these results in a sensitivity analysis to test the robustness of the IPD findings. Furthermore, the equivalent to the well-known Funnel plot can be visually assessed.

Additionally, subgroup analyses are planned for:

- patients undergoing non-emergent CABG vs patients undergoing urgent / emergent CABG because of ACS and

- patients preoperatively presenting with anaemia according to the World Health Organization-definition of less than 13 g/dL for men and less than 12 g/dL for women vs preoperatively non-anaemic patients.

Furthermore, sensitivity analyses will test the robustness of our findings for the analysis of the primary outcome. They will be performed for study quality and drug-specific preoperative withdrawal periods for each single day of withdrawal, including no preoperative withdrawal.

The analyses will be performed using a current version of R. No imputation for missing data is planned. The analyses are performed in accordance with the handbook of the Cochrane collaboration and results will be presented according to the PRISMA-IPD statement. [23]

Legend to figure 1 Flow chart diagram presenting the selection of articles for systemic review and meta-analysis of incidence of BARC-4 bleeding depending on type of $P2Y_{12}$ receptor inhibitor and preoperative withdrawal period.

Ethics and dissemination

This IPD-MA consists of secondary analyses of existing non-identifiable data and meets the criteria for waiver of ethics review by the local Research Ethics Committee. Data sharing and transfer will be subject to a confidentiality agreement and a data use agreement. Findings will be disseminated through peer-reviewed publication and conference presentation.

Contributors

Schoerghuber: study design, bibliographic research, design of data entry forms, data management, conduct of study, protocol and manuscript writing

Pregartner: study design, data management, statistical analysis, protocol and manuscript writing and review

Berghold: study design, data management, study design, data management, statistical analysis, protocol and manuscript review

Lindenau: bibliographic research, design of data entry forms, data management, conduct of study, protocol and manuscript review

Zweiker: Scientific coordination, protocol and manuscript writing and review

Voetsch: Scientific coordination, protocol and manuscript review

Mahla: study design, scientific coordination, protocol and manuscript writing and review

Zirlik: Scientific coordination, protocol and manuscript review

Funding

Competing interests

Michael Schoerghuber no conflicts of interest

Gudrun Pregartner no conflicts of interest

Andrea Berghold no conflicts of interest

Ines Lindenau no conflicts of interest

Robert Zweiker no conflicts of interest

Andreas Voetsch no conflicts of interest

Elisabeth Mahla no conflicts of interest

Andreas Zirlik received honoraria for lectures and consulting of Daiichi Sankyo, Lilly,

AstraZeneca, Bristol Myers Squibb, Pfizer, Bayer, Boehringer Ingelheim

Patient and public involvement

Patients and / or the public were not involved in the design, conduct, reporting or

dissemination plans of this research

Patient consent for publication

Not applicable

Provenance and peer review

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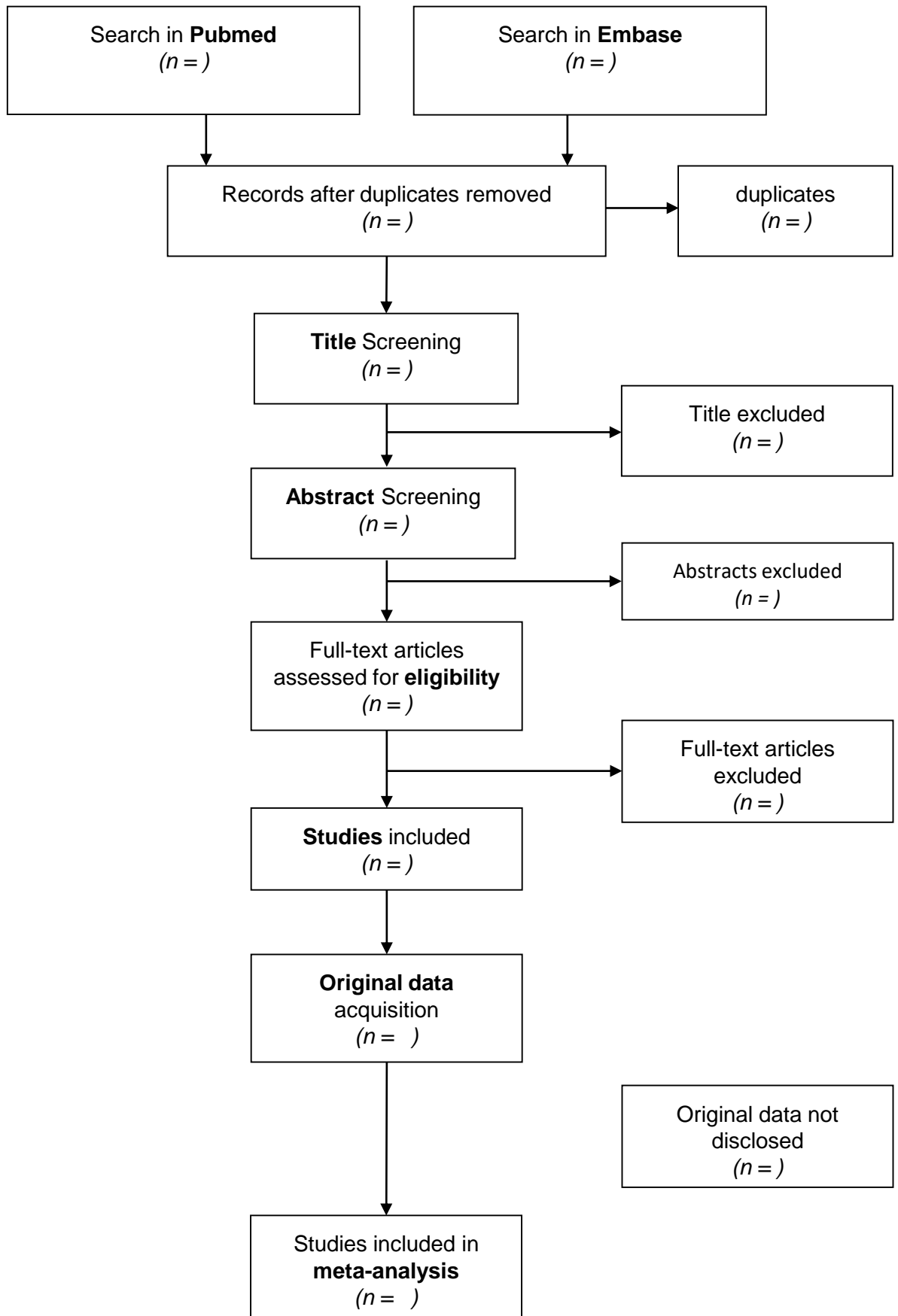Academic Research Consortium. *Circulation* 2011;123(23):2736-47. doi: 10.1161/CIRCULATIONAHA.110.009449

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Identification

Screening

Eligibility

Included

Search in **Pubmed**
(n =)

Search in **Embase**
(n =)

Records after duplicates removed
(n =)

duplicates
(n =)

Title Screening
(n =)

Title excluded
(n =)

Abstract Screening
(n =)

Abstracts excluded
(n =)

Full-text articles
assessed for **eligibility**
(n =)

Full-text articles
excluded
(n =)

Studies included
(n =)

Original data
acquisition
(n =   )

Original data not
disclosed
(n =)

Studies included in
meta-analysis
(n =   )

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	17
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8-9
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-14
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	13-14

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	13-14
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	14-15
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2 , Kendall's τ)	15-16
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	4
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6-7

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.